REMARKS

Claims 21 and 23-32 were pending. Claims 30-32 are canceled herein. Claims 21 and 23-29 are pending. No claim is allowed.

Applicants cancel claims 30-32 herewith. Applicants expressly reserve the right to pursue the subject matter of these claims in a related application.

Objections to the Specification

The Office objected to the abstract because it recited the word "said". The abstract has been amended to address this issue.

Applicants have reviewed the specification for the use of trademarks. Appropriate correction has been made. Applicants are unaware of any rule that requires that amendments be made in the specification as filed rather than the published application. Applicants would appreciate the Examiner providing the basis in the rules for this objection.

Rejection Under 35 U.S.C. §101 and § 112, first paragraph

Claims 21-29 remain rejected under 35 U.S.C. § 101 and § 112, first paragraph because the claimed invention allegedly is not supported by either a credible, specific, or substantial asserted utility or a well established utility for reasons of record. In particular, the Office alleged that the specific expression of the claimed FDF03 protein (SEQ ID NO:2) on a discrete cell population is a utility that is not in "mature form" such that it can readily be used in a real world sense. According to the Examiner, the overwhelming objective evidence demonstrating physiological activity of the FDF03 protein is insufficient to fulfill the utility requirement. Moreover, the Examiner asserts that Applicants have not established a probative relationship between the submitted evidence and the originally disclosed properties of the claimed invention. Applicants traverse this rejection for reasons of record as well as those discussed below.

In rejecting the presently claimed compositions, the Office has apparently taken the position that only certain evidence substantiated by actual experimental data establishes a patentable utility.

However, such is not the legal standard for the utility requirement. A disclosed utility for the claimed subject matter satisfies the utility requirement under § 101 absent evidence which would cast doubt on the objective truth of the disclosed utility. *Manual of Patent Examination Procedure* (hereinafter "M.P.E.P.") § 2107.02 (III)(A) (8th ed., Rev. 4, 2006). There is no legal requirement that the disclosed utility must be supported by conclusive experimental data. According to the M.P.E.P.,

> [a]s a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

M.P.E.P. § 2107.02 (III) (A), at page 2100-39 (emphasis original)(citations omitted). An applicant is only required to provide evidence that, when considered as a whole, leads the skilled artisan to conclude that the asserted utility is more likely than not true. *See* M.P.E.P. § 2107.03 (II).

Applicants respectfully submit that the Office has adopted an incorrect standard in maintaining the instant rejection. Specifically, the Office is requiring that a certain and exact disclosure of the biological role of the FDF03 protein and its significance must be described if the specification is to fulfill the utility requirement of §§ 101 and 112. In essence, the Office is requiring proof beyond a reasonable doubt regarding the functional role of the FDF03 protein in monocytes and cells of the myelomonocytic lineage. However, such is not the correct legal standard for utility.

While only one well-established utility is required, the specification discloses more than one specific, substantial and credible utility that satisfies the requirements of §§ 101 and 112. First, the specification disclosed that the FDF03 protein "likely plays a role in regulation or development of hematopoietic cells, ... *e.g.*, antigen presentation and the resulting effector functions." *See* the specification at page 68, line 37 to page 69, line 3. As discussed below, FDF03 is shown to play a role in mast cells and antigen presenting cells. Second, the specification discloses FDF03 as a cell surface marker that is discretely and specifically expressed on cells of the myelomonocytic lineage, *e.g.*, monocytes. *See* the specification at *e.g.*, page 54, lines 18-22 and page 87, line 35 to page 88, line 6. Any one of these utilities fulfills the utility requirement.

Regulation of Hemopoietic Cells including Antigen Presenting Cells

FDF03 has a specific, substantial and credible utility as a regulator of antigen presentation. Based on analysis of structural features, the specification discloses that FDF03 is an Ig receptor superfamily member. *See* the specification at page 42, lines 27-31. It is well accepted that "the Ig receptor superfamily constitutes a large number of cell proteins involved in the immune system and cellular recognition." *See* de Vet et al., *J. Biol Chem.* (2001) 276:42070, first paragraph (already of record) (*citing* Hunkapiller et al. *Adv. Immunol.* (1989) 44:1-63 and Williams et al., *Ann. Rev. Immunol.* (1988) 6:381-405). The specification further discloses the restricted expression of FDF03 to cells of the myelomonocytic lineage. *See* the specification at *e.g.*, page 54, lines 18-22 and page 87, line 35 to page 88, line 6. In view of the restricted expression and known functions of the Ig receptor superfamily, the specification identifies a specific utility for FDF03 as a regulator of hematopoietic cells including those involved in antigen presentation (*e.g.*, monocytes and dendritic cells). *See* the specification at page 68, line 35 to page 69, line 3.

The objective evidence already of record provides unassailable support of this utility as one that is specific, substantial, and credible. In brief, the objective evidence demonstrates that FDF03 is a receptor that regulates the activation of cells in the myeloid lineage, particularly monocytes and dendritic cells. Monocytes upon activation typically differentiate into macrophages which can act as antigen presenting cells. Dendritic cells are "professional" or specialized antigen presenting cells that must be activated prior to presenting antigen to other cells. *See, e.g.*, Exhibit A. Applicants provided 14 different references with the Amendment in Response to Non-Final Office Action dated January 10, 2006 that recognize and/or demonstrate that the FDF03 negatively regulates, *i.e.*, inhibits, activation of dendritic cells and monocytes. *See, e.g.*, Toyama-Sorimarchi, et al., *J. Immunol.* (2005) 174:4621, 4622 (already of record) (stating that dendritic cells ("DCs") express inhibitory receptors such as FDF03 play crucial roles in DC function). Regulating dendritic cells through inhibition of activation is specific and substantial in its real world use as a modulator of antigen presentation[1] and the resulting effector functions. Given the role of Ig receptor superfamily proteins known in the art and the structural data disclosed in the specification, the utility of

[1] As the activation state of antigen presenting cells is inextricably linked to antigen presentation capacity of these cells, a person of ordinary skill in the art would find such a utility credible. *See, e.g.*, Exhibit B (discussing the activation requirement for monocytes to function in immune responses).

regulating hematopoietic cells including those that act as antigen presentation cells is a credible utility to one of skill in the art.

The dendritic cell data provided is sufficient because only a minimal utility is required. There is no legal requirement for definitive evidence and disclosure of the exact mechanism and function of FDF03 in the regulation of cells of the myeloid lineage or in antigen presentation. Because the threshold of utility is minimal under 35 U.S.C. § 101, an invention is useful if it is *merely* capable of providing some identifiable benefit. *Juicy Whip, Inc. v. Orange Bang, Inc.*, 51 U.S.P.Q.2d 1700, 1702 (Fed. Cir. 1999) (*citing Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Therefore, the character and amount of evidence required is determined by what is claimed and whether it contravenes established scientific principle and belief. The evidence disclosed in the instant specification is in a sufficient amount and is supported by the objective evidence of record, thus fulfilling the utility requirement.

Regulation of Hematopoietic Cells, *e.g.*, Mast Cells

FDF03 has a specific, substantial and credible utility as a regulator of hematopoietic cells which include mast cells. As previously discussed, the objective evidence demonstrates that antibodies against the FDF03 protein inhibit the degranulation of mast cells. To date, the Examiner has offered no evidence which cast doubt on the objective truth of the evidence presented in Dr. Phillips declaration. Nor has the Examiner argued that the ability to regulate hematopoietic cells itself lacks utility. The Examiner acknowledges the ability of FDF03 to regulate mast cells, but instead finds that it is not sufficiently specific and substantial because "many other proteins also play a role in the regulation of immunological response produced from immune cells." *See* Action dated April 5, 2006 at page 8. However, the relative ability of other proteins to regulate immune responses is irrelevant to the utility analysis. It is the recognition that FDF03 regulates hematopoietic cells together with the supporting objective evidence that gives the protein its utility, not whether or not its full potential or any exact mechanism of action was elucidated and disclosed. "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." *In re Brana*, 51 F.3d 1560, 1568, 34 U.S.P.Q.2d 1436, 1442 (Fed. Cir. 1995). In other words, a requirement for a certain "maturity" of a claimed protein, particularly with regard to its ultimate therapeutic uses, has no legal basis

under the utility standard of 35 U.S.C. § 101. The claimed must merely be useful in a specific, substantial and credible fashion. FDF03 role in hematopoietic regulation, *e.g.*, regulating mast cell activity, is specific, substantial in its real world use of modulating immune responses involving mast cell degranulation, and credible based on the objective evidence in Dr. Phillips' declaration.

Marker for Cells of the Myelomonocytic Lineage including Monocytes

FDF03 has a specific, substantial and credible utility as a diagnostic marker on cells of myelomonocytic lineage for reasons already of record. Briefly, the specification discloses the restricted expression of FDF03 and indicates that this restricted expression makes it useful as a diagnostic marker. *See* the specification at *e.g.*, page 54, lines 18-22, page 87, line 35 to page 88, line 6, and page 88, line 29 to page 89, line 4. To date, the Examiner has not challenged the validity of this utility. However, the Examiner maintains that the specification is deficient in that it allegedly does not disclose a sufficient biological role of the FDF03 protein or its significance. Applicants disagree with the assertion that the biological role of FDF03 was not disclosed for reasons discussed above. Nonetheless, Applicants note that the utility of FDF03 as an identifier of a specific cell population is sufficiently specific, substantial and credible to meet the utility requirement without disclosing a biological role or its significance. As stated above, there is no requirement for definitive evidence and disclosure of a detailed biologic profile for a protein to satisfy the utility requirement. The utility must *merely* capable of providing some identifiable benefit. Dendritic cells are recognized as the most potent of antigen presenting cells in the art. Therefore, the ability to use FDF03 as a marker for dendritic cells provides an identifiable benefit to the researcher or the physician. Greater sophistication in cell identification using such markers assists the researcher in, for example, cell separation applications and the physician in increasing diagnostic strength in dendritic cell-based diseases. Therefore, the utility as a marker for myelomonocytic cells in general, and dendritic cells in particular, satisfies the utility requirement as it is specific, substantial and credible.

Finally, Applicants respectfully submit that the law does not require the certain and exact data on biological role or function demanded by the Examiner. The Board of Patent Appeals and Interference ("the Board") recently acknowledged the absence of such a requirement in *Ex parte*

Hedrick. *See* Exhibit C. In *Ex parte* Hedrick, the Board considered an application claiming a compound that bound a novel cytokine (*e.g.*, an antibody). The specification disclosed that the cytokine played a role in inflammation based (at least in part) on structural and sequence similarities between the cytokine and the IL-1 family of cytokines. The claims were rejected under 35 U.S.C. § 101. Applicants provided post-filing evidence that the novel cytokine played a role in psoriasis, an inflammatory condition of the skin. The Examiner maintained the rejection, alleging that disclosure that the cytokine played a role in inflammation was insufficient as (1) many compounds play a role in inflammation, (2) psoriasis was not specifically disclosed as an inflammatory condition where the cytokine acted, and (3) the precise function of the cytokine in psoriasis was not disclosed.

Upon Appeal, the Board reversed the examiner's utility rejection and held that the specification satisfied the utility requirement. According to the Board,

> [once] it is accepted that the [cytokine] either contributed to or inhibits the inflammatory response, it seems likely that those skilled in the art would recognize the claimed binding compounds are useful for either inhibiting or promoting inflammation. The examiner has not argued that compounds that promote inflammation lack utility, or that compounds that inhibit inflammation lack utility. Since the examiner apparently accepts the claimed compounds will have one of these two activities, the disclosure that IL-1δ has a role in inflammation seems adequate to support utility.

See Exhibit C at page 10. Moreover, the Board held that the post-filing evidence was acceptable because it was used to show the accuracy of the utility disclosed in the specification. *See id.* at pages 10-11. The Board then noted that pharmaceutical inventions necessarily include the expectation of further research and development. *See id.* at page 11.

The facts in the instant application are very similar to those of the Board decision discussed in *Ex parte* Hedrick. The specification discloses a discrete expression pattern of FDF03 in myeloid cells (including dendritic cells) and a structural similarity to the Ig receptor superfamily, a family of receptors known to play critical roles in immune responses and cellular recognition. The specification discloses a role for FDF03 in regulation or development of hematopoietic cells, for example, the regulation of antigen presentation and resulting effector functions. Objective evidence demonstrates that FDF03 plays a role in the regulation of mast cells (*i.e.*, hematopoietic cells) and

dendritic cells (*i.e.*, hematopoietic cells that are antigen presenting cells) as disclosed in the specification. Nothing more is required to meet the utility requirement.

As the specification provides adequate utility for the reasons discussed above, Applicants submit that the specification also provides sufficient written description on how to use the claimed FDF03 polypeptide.

For at least these reasons, Applicants respectfully submit that the rejection under 35 U.S.C. §§ 101 and 112 are overcome and should be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 140942001311. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: September 5, 2006

Respectfully submitted,

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immunobiology 5

THE IMMUNE SYSTEM IN HEALTH AND DISEASE

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Inflammation is traditionally defined by the four Latin words *calor, dolor, rubor,* and *tumor,* meaning heat, pain, redness, and swelling, all of which reflect the effects of cytokines and other inflammatory mediators on the local blood vessels. Dilation and increased permeability of the blood vessels during inflammation lead to increased local blood flow and the leakage of fluid, and account for the heat, redness, and swelling. Cytokines and complement fragments also have important effects on the adhesive properties of the endothelium, causing circulating leukocytes to stick to the endothelial cells of the blood vessel wall and migrate between them to the site of infection, to which they are attracted by chemokines. The migration of cells into the tissue and their local actions account for the pain. The main cell types seen in an inflammatory response in its initial phases are neutrophils, which are recruited into the inflamed, infected tissue in large numbers. Like macrophages, they have surface receptors for common bacterial constituents and complement, and they are the principal cells that engulf and destroy the invading microorganisms. The influx of neutrophils is followed a short time later by monocytes that rapidly differentiate into macrophages. Macrophages and neutrophils are thus also known as **inflammatory cells**. Inflammatory responses later in an infection also involve lymphocytes, which have meanwhile been activated by antigen that has drained from the site of infection via the afferent lymphatics.

The innate immune response makes a crucial contribution to the activation of adaptive immunity. The inflammatory response increases the flow of lymph containing antigen and antigen-bearing cells into lymphoid tissue, while complement fragments on microbial surfaces and induced changes in cells that have taken up microorganisms provide signals that synergize in activating lymphocytes whose receptors bind to specific microbial antigens. Macrophages that have phagocytosed bacteria and become activated can also activate T lymphocytes. However, the cells that specialize in presenting antigen to T lymphocytes and initiating adaptive immunity are the dendritic cells.

1-6 Activation of specialized antigen-presenting cells is a necessary first step for induction of adaptive immunity.

The induction of an adaptive immune response begins when a pathogen is ingested by an **immature dendritic cell** in the infected tissue. These specialized phagocytic cells are resident in most tissues and are relatively long-lived, turning over at a slow rate. They derive from the same bone marrow precursor as macrophages, and migrate from the bone marrow to their peripheral stations, where their role is to survey the local environment for pathogens. Eventually, all tissue-resident dendritic cells migrate through the lymph to the regional lymph nodes where they interact with recirculating naive lymphocytes. If the dendritic cells fail to be activated, they induce tolerance to the antigens of self that they bear.

The immature dendritic cell carries receptors on its surface that recognize common features of many pathogens, such as bacterial cell wall proteoglycans. As with macrophages and neutrophils, binding of a bacterium to these receptors stimulates the dendritic cell to engulf the pathogen and degrade it intracellularly. Immature dendritic cells are also continually taking up extracellular material, including any virus particles or bacteria that may be present, by the receptor-independent mechanism of **macropinocytosis**. The function of dendritic cells, however, is not primarily to destroy pathogens but to carry pathogen antigens to peripheral lymphoid organs and there present them to T lymphocytes. When a dendritic cell takes up a pathogen in infected tissue, it becomes activated, and travels to a nearby lymph node. On activation,

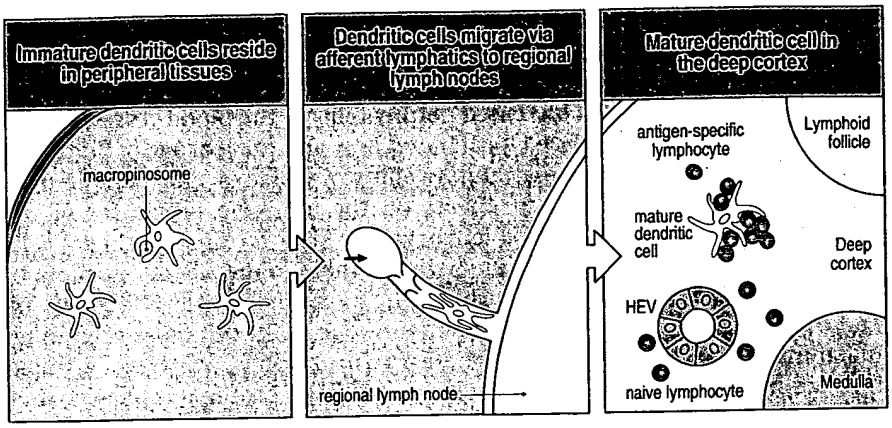

Fig. 1.13 Dendritic cells initiate adaptive immune responses. Immature dendritic cells resident in infected tissues take up pathogens and their antigens by macropinocytosis and receptor-mediated phagocytosis. They are stimulated by recognition of the presence of pathogens to migrate via the lymphatics to regional lymph nodes, where they arrive as fully mature nonphagocytic dendritic cells. Here the mature dendritic cell encounters and activates antigen-specific naive T lymphocytes, which enter lymph nodes from the blood via a specialized vessel known from its cuboidal endothelial cells as a high endothelial venule (HEV).

the dendritic cell matures into a highly effective **antigen-presenting cell** (APC) and undergoes changes that enable it to activate pathogen-specific lymphocytes that it encounters in the lymph node (Fig. 1.13). Activated dendritic cells secrete cytokines that influence both innate and adaptive immune responses, making these cells essential gatekeepers that determine whether and how the immune system responds to the presence of infectious agents. We shall consider the maturation of dendritic cells and their central role in presenting antigens to T lymphocytes in Chapter 8.

1-7 Lymphocytes activated by antigen give rise to clones of antigen-specific cells that mediate adaptive immunity.

The defense systems of innate immunity are effective in combating many pathogens. They are constrained, however, by relying on germline-encoded receptors to recognize microorganisms that can evolve more rapidly than the hosts they infect. This explains why they can only recognize microorganisms bearing surface molecules that are common to many pathogens and that have been conserved over the course of evolution. Not surprisingly, many pathogenic bacteria have evolved a protective capsule that enables them to conceal these molecules and thereby avoid being recognized and phagocytosed. Viruses carry no invariant molecules similar to those of bacteria and are rarely recognized directly by macrophages. Viruses and encapsulated bacteria can, however, still be taken up by dendritic cells through the nonreceptor-dependent process of macropinocytosis. Molecules that reveal their infectious nature may then be unmasked, and the dendritic cell activated to present their antigens to lymphocytes. The recognition mechanism used by the lymphocytes of the adaptive immune response has evolved to overcome the constraints faced by the innate immune system, and enables recognition of an almost infinite diversity of antigens, so that each different pathogen can be targeted specifically.

Instead of bearing several different receptors, each recognizing a different surface feature shared by many pathogens, each naive lymphocyte entering the bloodstream bears antigen receptors of a single specificity. The specificity of these receptors is determined by a unique genetic mechanism that operates during lymphocyte development in the bone marrow and thymus to generate millions of different variants of the genes encoding the receptor molecules. Thus, although an individual lymphocyte carries receptors of only one specificity, the specificity of each lymphocyte is different. This ensures that the millions of lymphocytes in the body collectively carry millions of

Cellular and Molecular Immunology

Fifth Edition

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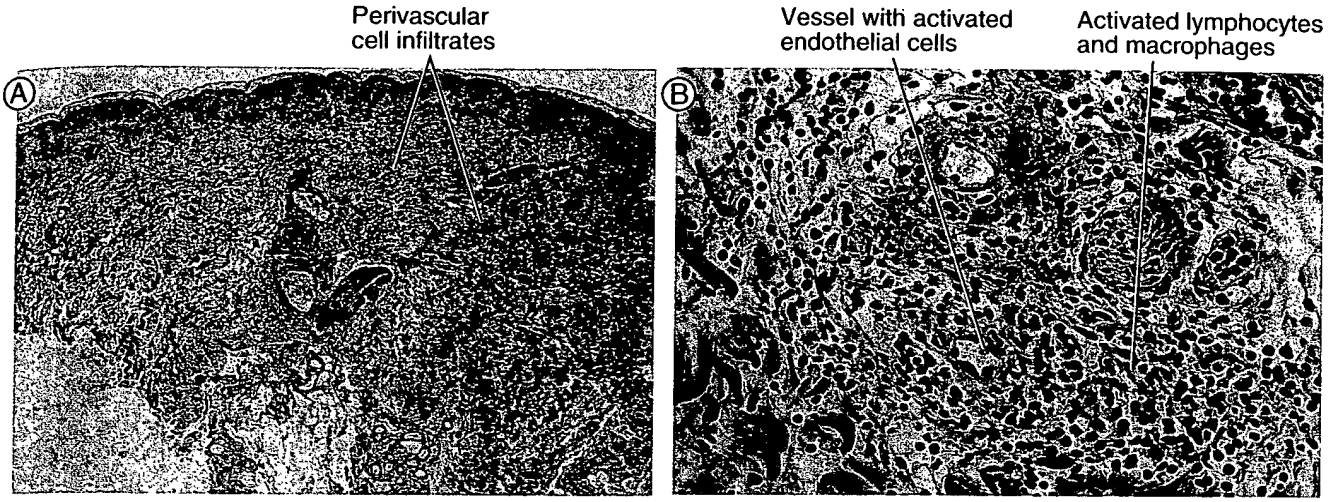


Figure 13–13 Morphology of a delayed-type hypersensitivity reaction.
Histopathologic examination of the reaction illustrated in Figure 13–12 shows perivascular mononuclear cell infiltrates in the dermis (A). At higher magnification, the infiltrate is seen to consist of activated lymphocytes and macrophages surrounding small blood vessels in which the endothelial cells are also activated (B). (Courtesy of Dr. J. Faix, Department of Pathology, Stanford University School of Medicine, Palo Alto, Calif.)

cule, CD44, which is also expressed at high levels on effector and memory T cells, binds to hyaluronate. As a result, antigen-specific effector and memory T cells that encounter the antigen are preferentially retained at the extravascular site where the antigen is present. T cells not specific for the antigen may return through lymphatic vessels to the circulation.

Effector Mechanisms of Cell-Mediated Immunity

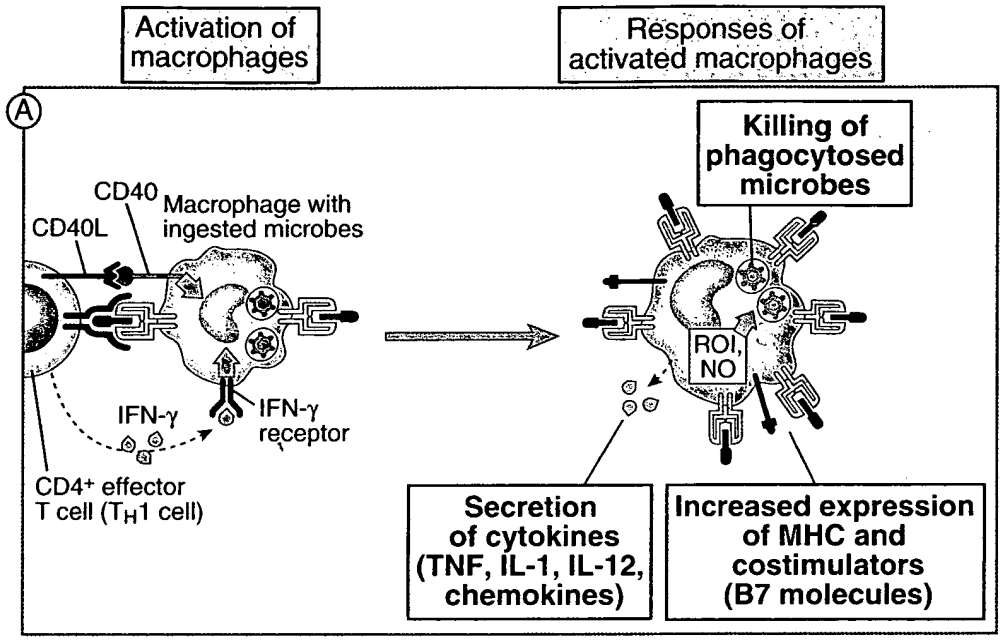
After effector T cells migrate to peripheral sites of infection or antigen challenge and recognize the antigen for which they are specific, the cells are activated to perform their effector functions. In CMI, the principal effector function of $CD4^+$ T cells is to stimulate the microbicidal activities of macrophages and other leukocytes, and the effector functions of $CD8^+$ CTLs are to kill infected cells and activate phagocytes.

T Cell–Mediated Activation of Macrophages and Other Leukocytes

Activated macrophages are the effector cells of CMI that function to eliminate phagocytosed microbes. Monocytes are recruited from blood into tissues and are exposed to signals from T_H1 effector cells and $CD8^+$ effector cells responding to antigen in the tissues. This interaction results in conversion of the monocytes to activated macrophages that are able to kill microbes. Activation consists of quantitative changes in the expression of various proteins that endow activated macrophages with the capacity to perform some functions that cannot be performed by resting monocytes. A macrophage is considered to be activated if it performs a function measured in a specific assay, for example, microbial killing. In the following sections, we describe the T cell signals that activate macrophages in cell-mediated immune reactions and the effector functions of these macrophages.

Stimuli for Macrophage Activation

$CD4^+$ T_H1 and $CD8^+$ T cells activate macrophages by contact-mediated signals delivered by CD40L-CD40 interactions and by the cytokine IFN-γ (Fig. 13–14). (Recall that helper T cells stimulate B lymphocyte proliferation and differentiation also by CD40-mediated signals and cytokines; see Chapter 9, Fig. 9–10.) When effector T_H1 cells and $CD8^+$ T cells are stimulated by antigen, the cells secrete cytokines, notably IFN-γ, and they express CD40L. IFN-γ is the major macrophage-activating cytokine. It activates some macrophage responses by itself and functions together with bacterial LPS or CD40 signals to elicit other responses. Knockout mice lacking IFN-γ or the IFN-γ receptor are extremely susceptible to infection by intracellular microbes. CD40L engages CD40 on macrophages that are presenting antigen to the T cells and activates an intracellular signal transduction pathway that is similar to the pathway activated by TNF receptors (see Chapter 11, Box 11–1). The importance of CD40 in macrophage activation is demonstrated by the immunologic defects in humans with inherited mutations in CD40L (**X-linked hyper-IgM syndrome**) and mice in which the gene for CD40 or CD40L is knocked out (see Chapter 20). All these disorders are characterized by severe deficiencies in CMI to intracellular microbes, and children with the X-linked hyper-IgM syndrome often succumb to infection by the intracellular pathogen *Pneumocystis carinii*. As expected, these patients and knockout mice also have defects in helper T cell–dependent antibody



B

Macrophage response	Role in cell-mediated immunity
Production of reactive oxygen intermediates, nitric oxide, increased lysosomal enzymes	Killing of microbes in phagolysosomes (effector function of macrophages)
Secretion of cytokines (TNF, IL-1, IL-12)	TNF, IL-1: leukocyte recruitment (inflammation) IL-12: T_H1 differentiation, IFN-γ production
Increased expression of B7 costimulators, MHC molecules	Increased T cell activation (amplification)

Figure 13–14 Activation and functions of macrophages in cell-mediated immunity.
In cell-mediated immunity, macrophages are activated by CD40L-CD40 interactions and by IFN-γ and perform several functions that kill microbes, stimulate inflammation, and enhance the antigen-presenting capacity of the cells. Macrophages are also activated during innate immune reactions and perform the same functions (see Chapter 12, Fig. 12–5).

production. The requirement for CD40L-CD40 interactions for macrophage activation ensures that macrophages that are presenting antigens to the T cells (i.e., the macrophages that are harboring intracellular microbes) are also the macrophages that are most efficiently activated by the T cells. $CD8^+$ T cells can activate macrophages by the same mechanisms and with the same functional outcomes. In this case, the T cells recognize microbial antigens that are present in the cytosol of the antigen-presenting macrophages. In innate immune reactions, the same process of macrophage activation is triggered by microbial products such as LPS, which turn on some of the same biochemical pathways as CD40, and by IFN-γ secreted by NK cells (see Chapter 12).

Functions of Activated Macrophages

In response to CD40 signals and IFN-γ, production of several proteins in macrophages is increased. CD40 ligation activates the transcription factors NF-κB and AP-1, and IFN-γ activates the transcription factors STAT1 and IRF-1. As a result of these signals, activated macrophages produce increased amounts of the proteins that are responsible for the effector functions of these cells in CMI (see Fig. 13–14). The effector functions of activated macrophages include the following.

- ***Activated macrophages kill phagocytosed microbes, mainly by producing microbicidal reactive oxygen intermediates, nitric oxide, and lysosomal enzymes.*** The microbicidal mechanisms of macrophages were described in Chapter 12. To reiterate the key points, macrophage activation leads to increased synthesis of reactive oxygen intermediates and nitric oxide, which are potent microbicidal agents that are produced within the lysosomes of macrophages and kill ingested microbes. Activated macrophages contain increased amounts of lysosomal enzymes, which destroy phagocytosed microbes after phagosomes fuse with lysosomes. Reactive

oxygen intermediates, nitric oxide, and lysosomal enzymes may also be released into adjacent tissue, where they kill extracellular microbes and may cause damage to normal tissue.

- Activated macrophages stimulate acute inflammation through the secretion of cytokines, mainly TNF, IL-1, and chemokines, and short-lived lipid mediators such as platelet-activating factor, prostaglandins, and leukotrienes. The collective action of these macrophage-derived cytokines and lipid mediators is to produce a local inflammation that is rich in neutrophils, which phagocytose and destroy infectious organisms.
- Activated macrophages (and neutrophils) remove dead tissues to facilitate repair after the infection is controlled. Activated macrophages also induce the formation of repair tissue by secreting growth factors that stimulate fibroblast proliferation (platelet-derived growth factor), collagen synthesis (transforming growth factor-β), and new blood vessel formation or angiogenesis (fibroblast growth factor). Thus, the activated macrophage acts as an endogenous surgeon to cauterize the wound and thereby eliminate antigen and resolve the inflammatory reaction.

Even though macrophages can respond directly to microbes in innate immune reactions, the ability of macrophages to kill ingested microorganisms is greatly enhanced by T cells. This is why CMI is able to eradicate microbes that have evolved to survive within macrophages in the absence of adaptive immunity. In addition to these effector functions, activated macrophages become more efficient APCs because of increased levels of molecules involved in antigen processing (such as components of the proteasome and cathepsins), increased surface expression of class II MHC molecules and costimulators, and production of cytokines (such as IL-12) that stimulate T lymphocyte proliferation and differentiation. These macrophage responses function to enhance T cell activation, thus serving as amplification mechanisms for CMI.

Some tissue injury may normally accompany cell-mediated immune reactions to microbes because the microbicidal products released by activated macrophages and neutrophils are capable of injuring normal tissue and do not discriminate between microbes and host tissue. However, this tissue injury is usually limited in extent and duration, and it resolves as the infection is cleared. If the activated macrophages fail to eradicate the infection, they continue to produce cytokines and growth factors, which progressively modify the local tissue environment. As a result, tissue injury is followed by replacement with connective tissue (fibrosis), and fibrosis is a hallmark of chronic DTH reactions. In chronic DTH reactions, activated macrophages also undergo changes in response to persistent cytokine signals. These macrophages develop increased cytoplasm and cytoplasmic organelles and histologically may resemble skin epithelial cells, because of which they are sometimes called epithelioid cells. Activated macrophages may fuse to form multinucleate giant cells. Clusters of activated macrophages, often surrounding particulate sources of antigen, produce nodules of inflammatory tissue called granulomas (Fig. 13–15). Granulomatous inflammation is a characteristic response to some persistent microbes, such as *M. tuberculosis* and some fungi, and represents a form of chronic DTH. Granulomatous inflammation is frequently associated with tissue fibrosis. Although fibrosis is normally a "healing reaction" to injury, it can also interfere with normal tissue function. In fact, much of the respiratory difficulty associated with tuberculosis or chronic fungal infection of the lung is caused by replacement of normal lung with fibrotic tissue and not directly attributable to the microbes.

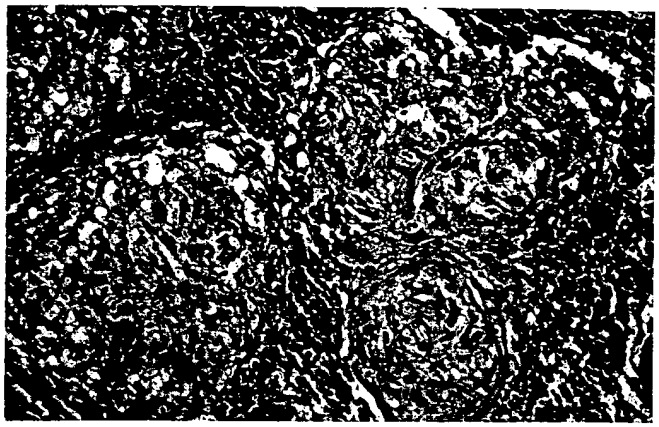


Figure 13–15 Granulomatous inflammation.
Histopathologic examination of a lymph node shows a granuloma with activated macrophages and lymphocytes. In some granulomas, there may be a central area of necrosis. Immunohistochemical studies would identify the lymphocytes as T cells. This type of inflammation is a chronic delayed-type hypersensitivity reaction against persistent microbial and other antigens. (Courtesy of Dr. Henry Sanchez, Department of Pathology, UCSF School of Medicine, San Francisco.)

Role of T_H2 Cells and Eosinophils in Defense Against Helminths

T_H2 cells induce inflammatory reactions that are dominated by eosinophils and mast cells (see Fig. 13–10). This type of immune response functions to eliminate helminthic infections and may play a role in defense against some ectoparasites. Helminths are too large to be phagocytosed and may be more resistant to the microbicidal activities of macrophages than are most bacteria and viruses. The immune response to helminths consists largely of T_H2 cells, which secrete IL-4, IL-5, and IL-13. IL-4 (and IL-13) stimulates the production of helminth-specific IgE antibodies, which opsonize the helminths. IL-5 activates eosinophils, which bind to the IgE-coated helminths by virtue of Fc receptors specific for the ε heavy chain. Activated eosinophils release their granule contents, including major basic protein and major cationic protein, which are capable of destroying even the tough integuments

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JOSEPH A. HEDRICK,
THEODORE R. SANA, J. FERNANDO BAZAN,
and ROBERT A. KASTELEIN

Appeal No. 2005-1922
Application No. 09/770,528

ON BRIEF

Before SCHEINER, MILLS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to compounds, such as antibodies, that bind a mouse interleukin-1 protein. The examiner has rejected the claims as lacking patentable utility. We have jurisdiction under 35 U.S.C. § 134. We reverse, because the evidence of record shows that the disclosed interleukin is likely to be involved in inflammation.

Background

The specification discloses "two novel mammalian, e.g., rodent interleukin-1 like molecules, designated interleukin-1δ (IL-1δ) and interleukin-1ε (IL-1ε). Both IL-1δ and IL-1ε exhibit both structural and sequence similarity, e.g., by homology comparison to known members of the IL-1 family of molecules." Page 5. The specification describes

the "complete nucleotide (SEQ ID NO:1) and corresponding amino acid sequence (SEQ ID NO:2) of a rodent IL-1δ coding segment." Page 16. See also page 22 (SEQ ID NO:2 is "mouse IL-1δ").

"Structural alignment of mouse IL-1δ and mouse IL-1ε with other members of the IL-1 family show[s] conserved features/residues, particularly 12 β strands folded into a β-trefoil fold." Page 40. "The solved structures for IL-1β, the natural IL-1 receptor antagonist (IL-1Ra), and a co-structure of IL1Ra/IL-1 receptor type I . . . suggest how to make a mouse IL-1δ or IL-1ε antagonist. . . . [T]he only known antagonist to IL-1 receptor (IL-1Ra . . .) is missing an amino acid domain bounded by the β4 and β5 strands. . . [,] suggesting that its absence confers antagonist activity." Page 41. "The corresponding loop in rodent IL-1δ or IL-1ε (between β4 and β5) defines a domain that forms a polypeptide loop which is part of a primary binding segment to the IL-1 receptor. . . . More precisely, the loop is defined for IL-1δ by amino [acid] residues Pro47-Ala53 of SEQ ID NO:2. . . . Accordingly, IL-1δ or IL-1ε antagonist activity should be generated by removal of all or an appropriate portion of amino acids located between β4 and β5." Page 42.

The specification discloses that "[t]he IL-1δ or IL-1ε proteins will have a number of different biological activities, e.g., in the immune system, and will include inflammatory functions or other innate immunity responses." Page 31. "The activities of the mouse IL-1α, IL-1β, and IL-1γ have been compared as to their activity to induce IFN-γ [interferon gamma]. . . . The IL-1γ was found to be much more potent in stimulating IFN-1γ [sic, IFN-γ] than either IL-1α or IL-1β. IL-1δ and IL-1ε and their agonists or antagonists should have related activities, typically affecting similar immune functions, including inflammatory responses." Id.

"The family of interleukins 1 contains molecules, each of which is an important mediator of inflammatory disease." Page 97. "IL-1δ or IL-1ε being homologous members of the IL-1 family . . . likely play a role in modulating of local and systemic inflammatory processes . . . , through the enhancement of blood flow, induction of chemoattractants, and the enhancement and adherence of adhesion molecules resulting in the accumulation of inflammatory cells such as macrophages and neutrophils at the site of inflammation." Page 79.

"IL-1δ or IL-1ε are also likely to play a role in systemic inflammatory reactions. . . . A systemic reaction such as septic shock involves vasodilation, due to IL-1, most likely in combination with other cytokines. . . . The newly described IL-1δ or IL-1ε are also likely to be similarly involved." Page 80.

Discussion

1. Claim construction

Claim 7, the only independent claim on appeal, reads as follows:

> 7. A binding compound comprising an antigen binding site from an antibody, which specifically binds to a mature polypeptide comprising at least 8 contiguous amino acid residues from SEQ ID NO:2, wherein said antigen binding site specifically binds an epitope located within said contiguous amino acid residues.

Claim 7 is directed to a binding compound comprising at least an antigen-binding site, where the antigen-binding site is from an antibody that specifically binds a "mature polypeptide" comprising at least eight contiguous amino acids of SEQ ID NO:2, and the epitope bound by the antigen-binding site is located within the contiguous amino acids from SEQ ID NO:2. Claim 7 therefore encompasses, among other things, antibodies that bind specifically to mouse IL-1δ (i.e., the protein having the amino acid sequence shown in SEQ ID NO:2).

2. Utility

The examiner rejected claims 7-9 and 20-25, all of the claims remaining, under 35 U.S.C. §§ 101 and 112, first paragraph, for lack of patentable utility. The examiner bears the initial burden of showing that a claimed invention lacks patentable utility. See In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) ("Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence.").

The Supreme Court addressed § 101's utility requirement in Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). The claimed invention in Brenner "a chemical process which yields an already known product whose utility—other than as a possible object of scientific inquiry—ha[d] not yet been evidenced." Id. at 529, 148 USPQ at 693. The Brenner Court held that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field." Id. at 534-35, 148 USPQ at 695.

The Court of Customs and Patent Appeals first applied Brenner in In re Kirk, 376 F.2d 936, 153 USPQ 48 (CCPA 1967). The invention claimed in Kirk was a set of steroid derivatives said to have valuable biological properties and to be of value "in the furtherance of steroidal research and in the application of steroidal materials to veterinary or medical practice." Id. at 938, 153 USPQ at 50. The court held that such uses did not satisfy § 101: "There can be no doubt that the insubstantial, superficial

nature of vague, general disclosures or arguments of 'useful in research' or 'useful as building blocks of value to the researcher' was recognized, and clearly rejected, by the Supreme Court" in Brenner. See Kirk, 376 F.2d at 945, 153 USPQ at 55.

More recently, the Federal Circuit held that § 101 was not satisfied by a disclosure that "solid granules of polypropylene could be pressed into a flexible film with a characteristic infrared spectrum and that the polypropylene was 'plastic-like.'" In re Ziegler, 992 F.2d 1197, 1203, 26 USPQ2d 1600, 1605 (Fed. Cir. 1993). "Ziegler did not assert any practical use for the polypropylene or its film, and Ziegler did not disclose any characteristics of the polypropylene or its film that demonstrated its utility." Id. "[A]t best, Ziegler was on the way to discovering a practical utility for polypropylene at the time of the filing." Id., 26 USPQ2d at 1605.

On the other hand, the CCPA reversed a rejection for lack of utility in In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980), where the claimed pharmaceutical compositions were disclosed to be useful in treating acute myeloblastic leukemia. The active ingredients in the compositions were closely related to compounds which were "well recognized in the art as valuable for use in cancer chemotherapy" and the evidence showed that the claimed compositions were effective in treating tumors in a mouse model. See id. at 1323-24, 206 USPQ at 887-88.

The Federal Circuit held in Cross v. Iizuka, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985), that in some circumstances, in vitro testing is sufficient to show utility. More specifically, evidence showing successful in vitro testing supplemented by similar in vitro and in vivo activities of structurally similar compounds was held to meet the requirements of § 101. Id. at 1051, 224 USPQ at 748.

Finally, in In re Brana, the Federal Circuit held that § 101 was satisfied by disclosure that the claimed compounds had higher antitumor activity than related compounds known to have antitumor activity and evidence of in vivo activity against tumors in a mouse model. See 51 F.3d at 1567, 34 USPQ2d at 1442.

Several lessons can be drawn from these cases. First, § 101's requirement that an invention be "useful" is not to be given its broadest reach, such that little or nothing of a chemical nature would be found to lack utility. See Brenner, 383 U.S. at 530, 148 USPQ at 694. Thus, not every "use" that can be asserted will be sufficient to satisfy § 101.

Rather, § 101 requires a utility that is "substantial", i.e., one that provides a specific benefit in currently available form. Brenner, 383 U.S. at 534-35, 148 USPQ at 695. Under this standard, § 101 is satisfied by pharmaceutical compositions useful for treating leukemia (Jolles); by evidence showing successful in vitro testing supplemented by similar in vitro and in vivo activities of structurally similar compounds (Cross); and by evidence showing in vivo antitumor activity in mice, combined with a disclosure that the claimed compounds had higher antitumor activity than a known, related compound (Brana).

By contrast, "vague, general disclosures or arguments of 'useful in research' or 'useful as building blocks of value to the researcher'" do not satisfy § 101 (Kirk). Likewise, disclosing polypropylene that is "plastic-like" and can be pressed into a flexible film showed that the applicant was "at best . . . on the way to discovering a practical utility for polypropylene at the time of the filing," but not yet there (Ziegler).

In this case, the examiner took the position that the "assertion that the disclosed IL-1δ protein has biological activities similar to known IL-1 polypeptides cannot be

accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities." Examiner's Answer, page 5. The examiner cited several examples of proteins that have different activities despite belonging to the same family of growth factors. Id., pages 5-6. The examiner also pointed to the specification's statement that the IL-1 "family of genes have been implicated in a broad range of biological functions," and Kumar's[1] disclosure that "IL-1δ is an antagonist of IL-1ε, even though both polypeptides belong to the IL-1 family." Id., page 5.

The examiner also cited several references as evidence that "the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases." Id., pages 7-8. She concluded that

> based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality for new members of cytokine or growth factor polypeptide families, the assertion that the IL-1δ polypeptide recited in the claims has activities similar to previously characterized IL-1 polypeptides is not substantial.

Id., page 8.

The examiner found the specification's statement that IL-1δ "likely play[s] a role in modulating of local and systemic inflammatory processes" to be nonspecific and insubstantial. See id. at pages 8-9. The examiner found the asserted use in therapy to be insubstantial because the specification does not state what role IL-1δ plays in inflammation or what type of inflammation involves IL-1δ. The examiner found the asserted utility to be nonspecific because "a diverse group of chemical and

[1] Kumar et al., "Identification and initial characterization of four novel members of the interleukin-1 family,"

environmental stimuli can be said to 'play a role in modulating of local and systemic inflammatory processes', including cytokines, aspirin, lye, scratches, and ice." Id., page 9.

Appellants argue that "the specification discloses at least one specific utility for IL-1δ in inflammation based on structural homology to the IL-1 family and supported by the evidence of record," and that this utility is both substantial and credible. Appeal Brief, page 7. In support of the specification's assertion that IL-1δ is involved in inflammation, Appellants rely on the structural similarity between IL-1δ and other members of the IL-1 family, and on evidence provided by the Kumar and Debets[2] references, which were published after the filing date of this application.

The examiner acknowledged that "[t]here is little doubt that IL-1δ is a new member of the IL-1 family of cytokines, and that all of the IL-1 polypeptides characterized to date play a role of some sort in inflammation," but noted that "these roles are diverse." Examiner's Answer, page 16. See also page 20:

> The specification merely states that IL-1δ is likely to play a role in modulating inflammation. It does not characterize that role. . . . Is it up-regulated or down-regulated during inflammation? Without this information, the skilled artisan would not know if it was desirable to identify drugs that agonize or antagonize IL-1δ as a treatment for inflammation. Does IL-1[δ] play a role in skin inflammation or pancreas inflammation, or inflammation of any other tissue? Without this information, the skilled artisan would have to conduct experiments to identify specific inflammatory responses that involve IL-1δ.

The examiner considered Appellants' post-filing evidence but found that it did not cure the asserted deficiencies. See the Examiner's Answer, page 17:

Journal of Biological Chemistry, Vol. 275, pp. 10308-10314 (2000).

[2] Debets et al., "Two novel IL-1 family members, IL-1δ and IL-1ε, function as an antagonist and agonist of NF-κB activation through the orphan IL-1 receptor-related protein 2," Journal of Immunology, Vol. 167, pp. 1440-1446 (2001).

> The assertion in the specification that IL-1δ is likely to play a role in the modulation of inflammation is not a specific assertion of utility. . . . The post-filing date references of Debets et al. and Kumar et al. constitute specific disclosures of what IL-1δ's role in inflammation is. Unfortunately, these specific roles are not asserted in the specification as originally filed.

See also page 24: "Debets et al. and Kumar et al. provide further characterization of the IL-1δ protein which provide a credible, specific and substantial utility for IL-1δ. This further characterization, however, is part of the act of invention and until it was undertaken, Appellant's claimed invention as disclosed in the specification as originally filed, was incomplete."

The issues raised by the examiner are important ones in the analysis of whether an invention is supported by an adequate utility. If a specification merely discloses that a protein may be involved in one of a multitude of biological activities, or may have some uncharacterized role in any of a variety of diseases, the disclosure may very well fail to meet the requirements of § 101.

In this case, however, we do not find the examiner's concerns to be warranted. The specification states that IL-1δ, to which the claimed product binds, is a member of the IL-1 family of cytokines. The specification also states that all known IL-1 family members play a role in inflammation. The examiner has agreed with both of these points. See the Examiner's Answer, page 16 ("There is little doubt that IL-1δ is a new member of the IL-1 family of cytokines, and that all of the IL-1 polypeptides characterized to date play a role of some sort in inflammation.").

The examiner's rejection, therefore, has little to do with the concerns she has expressed regarding the difficulty of predicting function from structure and the possibility that small changes in protein structure will result in large changes in function. Rather, the rejection seems to be based on the lack of disclosure regarding the specific role that

IL-1δ plays in inflammation – does it contribute to or inhibit inflammation? – and the specific tissue(s) in which it acts.

We do not find these concerns to be adequate to support the rejection. Once it has been accepted that IL-1δ either contributes to or inhibits the inflammatory response, it seems that those skilled in the art would recognize the claimed binding compounds as useful. Specifically, if IL-1δ contributes to inflammation, those skilled in the art would recognize the claimed compounds to be useful in inhibiting inflammation. On the other hand, if IL-1δ inhibits inflammation, those skilled in the art would recognize the claimed compounds to be useful in promoting inflammation.

Thus, it would seem that the examiner's acceptance of IL-1δ as having a role in inflammation would require recognizing that IL-1δ-binding compounds are useful for either inhibiting or promoting inflammation. The examiner has not argued that compounds that promote inflammation lack utility, or that compounds that inhibit inflammation lack utility. Since the examiner apparently accepts that the claimed compounds will have one of these two activities, the disclosure that IL-1δ has a role in inflammation seems adequate to support utility.

The examiner, in fact, has indicated that if the specification had included the more specific disclosures in the Kumar and Debets references, the claims would be supported by an adequate utility. See the Examiner's Answer, page 24. The examiner discounted the references, however, because they were published after this application's effective filing date. Id.

We agree with the examiner that utility must be shown as of the effective filing date. See In re Brana, 51 F.3d at 1567 n.19, 34 USPQ2d at 1441 n.19. However, post-filing evidence is acceptable where it is relied on, not to supplement the specification's

disclosure, but to show the accuracy or inaccuracy of a statement in the specification. See id.; see also In re Hogan, 559 F.2d 595, 605 n.17, 194 USPQ 527, 537 n.17 (CCPA 1977).

Here, we agree with Appellants that the post-filing evidence supports the utility disclosed in the specification. In particular, Debets provides evidence supporting the specification's disclosure that IL-1δ plays a role in inflammation. Debets shows that IL-1δ specifically antagonizes the activity of IL-1ε, inhibiting the inflammatory response that IL-1ε stimulates. See page 1443. Debets also discloses that expression of IL-1δ and IL-1ε is increased in psoriatic skin lesions, "confirm[ing] the involvement of these novel IL-1s in response to skin inflammation." Page 1445.

It is true that the specific involvement of IL-1δ in skin inflammation was not disclosed in the specification. However, "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." Brana, 51 F.3d at 1568, 34 USPQ2d at 1442.

Here, once IL-1δ is accepted as a mediator of inflammation, those skilled in the art would recognize compounds that inhibit IL-1δ to be useful. Granted, some experimentation remains to be done before an IL-1δ-binding compound could be used, for example, in therapy. However, determining whether IL-1δ promotes or inhibits inflammation and which tissue(s) it acts in would seem to be questions more of enablement than of utility. The issue of enablement has not been briefed in this case, but testing different tissues for expression of a single, known gene would not on its face seem to be an undue amount of experimentation for persons skilled in the relevant art.

Summary

The evidence of record supports the specification's disclosure that the claimed products are useful in either inhibiting or promoting inflammation. We therefore reverse the rejections under 35 U.S.C. §§ 101 and 112, first paragraph, for lack of patentable utility.

REVERSED

Toni R. Scheiner)
Administrative Patent Judge)
)
)
Demetra J. Mills) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
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